methods for hazard and risk assessment of chemicals. In particular, computational methods have become increasingly important for profiling environmental fate and evaluating toxicity of chemical compounds, which lead to risk assessment. Many of the currently available computational methods do not consider chemical reactivity and fate either in environment and biological compartments. In this paper, we will present a chemoinformatics approach for predicting chemical reactivity in metabolism and degradation reactions. Structural alerts on chemical reactivity can be used as indicators for safety issues due to reactivity. The application of reaction rules which combine reaction types with a physicochemical evaluation of the reactions allows a more sophisticated assessment of a chemical compound. The integration of the prediction of chemical reactivity into the workflow of the hazard and risk assessment process will be demonstrated. This paper will also report on two tools funded by ECB [1]: 1) START (Structural Alerts for Reactivity in Toxtree [2]); 2) CRAFT (Chemical Reactivity and Fate Tool implemented in Ambit [3]). [1] European Commission's Joint Research Centre (JRC), Consumer Product Safety and Quality (CPS&Q) Unit, formerly known as European Chemicals Bureau (ECB, http://ecb.jrc.it/). [2] An open source decision tree application to estimate toxic hazard (http://ambit.acad.bg/toxTree/) [3] An open source chemoinformatics data management system (http://ambit.acad.bg/)

PS 1124 QUANTITATIVE STRUCTURE TOXICITY RELATIONSHIPS (QSTR) MODELS FOR PREDICTING ACUTE/SUB-ACUTE AND SUB-CHRONIC/CHRONIC ADVERSE EFFECT LEVELS.

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An important step in dose-response assessment is the identification of a critical effect level. The measure of critical effect often is presented as a no-observed-adverse-effect level (NOAEL), or a lowest-observed-adverse-effect level (LOAEL). Quantitative Structure Toxicity Relationships (QSTR) models are mathematical models that may be used to predict toxicity from physical characteristics of a chemical structure. In this research, QSTR models were developed to estimate critical effect levels from chemical structure. The modeling focus was on machine learning methods, Random Forest, k-Nearest Neighbor, and Support Vector Machine, as well as models using Partial Least Squares. The models were built using over 2700 toxicity values and 472 unique chemicals. Models were built with three commercial descriptor sets (Dragon, MOE, Molconnz) and one descriptor set from the US EPA. The performance of each model was assessed using a validation set not used in model development. These models show that it is very reasonable to predict critical effect values from chemical structure based on predictions of the validation set. The mean absolute error of the log scaled LOAEL and NOAEL values was close to 0.5 across models, giving confidence in the order of magnitude of the predictions. In addition, the applicability domains of these models were also evaluated Among the fours modeling methods used, all methods, with the exception of PLS, performed equally well. The models can be used as an additional tool for dose-response assessment when experimental data pertaining to critical effect levels do not exist.
Disclaimer: This research does not necessarily represent the views of the U.S. Environmental Protection Agency.

PS 1125 COMBINATORIAL QSAR MODELING OF RAT ACUTE TOXICITY BY ORAL EXPOSURE.

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Few Quantitative Structure-Activity Relationship (QSAR) studies have successfully modeled large, diverse mammalian toxicity endpoints. In this study, we have applied a combinatorial QSAR approach in the development of robust and predictive models of chemical acute toxicity of rat by oral exposure. To this end, we have compiled a comprehensive dataset of 7385 compounds with their median lethal dose (LD50) values in the oral exposure test of rats. To compare the predictive power of our models with an available commercial toxicity predictor, we used the same training set of 3472 compounds as the TOPKAT (Toxicity Prediction by Komputer Assisted Technology) software. The remaining 3913 compounds which were not present in the TOPKAT training set were used as the external validation set for our toxicity models. We have developed 7 different types of QSAR LD50 models for the modeling set. The internal prediction accuracy for the modeling set ranged from 0.52 to 0.96 as measured by the leave-one-out cross-validation correlation coefficient (Q2). The prediction accuracy for the external validation set ranged from 0.24 to 0.70 (linear regression coefficient R2). The use of applicability domain threshold implemented in most models generally improved the external prediction accuracy but led to the decrease in chemical space coverage. Finally, several consensus models were developed by averaging the predicted LD50 for every compound using all 7 models. We find that consensus models afford higher prediction accuracy for the external validation dataset with the highest coverage as compared to individual constituent models. The best validated LD50 models developed by our collaboration can be used as reliable computational predictors of in vivo acute toxicity and will be made publicly available from the participating laboratories.

PS 1126 RESOLVIN E2 PROTECTS AGAINST ACETAMINOPHEN (AA)-INDUCED HEPATOTOXICITY.

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Ingestion of toxic doses of AA causes centrilobular hepatic necrosis. Evidence suggests inflammatory mediators released by cytotoxic macrophages contribute to the pathogenic process. Resolvins are naturally occurring anti-inflammatory mediators derived from eicosapentaenoic acid. They inhibit production of IL-1β, IL-12, TNFα and nitric oxide, and suppress leukocyte chemotaxis. In the present studies, we analyzed the protective effects of resolvins against AA-induced hepatotoxicity. Treatment of B6129F2 mice with AA (300 mg/kg, i.p.) induced hepatotoxicity resulting in increases in serum transaminase levels within 3 hr peaking at 24 hr. This was correlated with histological evidence of centrilobular hepatic necrosis. Pretreatment of the mice with resolvin E2 (RvE2) (50 μg/kg/day, i.p., 3 days) abrogated these effects. TNFα exerts its biologic activity by binding to two distinct cell surface receptors, TNFR1 and TNFR2. AA-induced hepatotoxicity was associated with increased expression of TNFR2 in the liver. This response was response was inhibited by RvE2 pretreatment of the mice. RvE2 also reduced hepatic expression of cyclooxygenase-2, which mediates the generation of proinflammatory eicosanoids. Heme oxygenase (HO-1) is a potent antioxidant known to protect against AA-induced liver injury. Western blotting and immunohistochemistry (IHC) demonstrated that HO-1 was up-regulated in livers of mice treated with AA. This was predominantly observed in liver macrophages. RvE2 treatment, by itself, also upregulated HO-1 in the liver, but had no effect on expression of this antioxidant in AA treated mice. Similarly, RvE2 upregulated levels of glutathione in the liver. These data suggest that RVE2 may be useful in mitigating AA-induced hepatotoxicity by its ability to block the generation or activity of inflammatory mediators and upregulate antioxidants (Supported by NIH GM034310 and ES005022).

PS 1127 S-ADENOSYLMETHIONINE (SAME) REVERSAL OF ACETAMINOPHEN (APAP) EFFECTS ON HEPATIC GLUTATHIONE PEROXIDASE AND HEPATIC SAME LEVELS.

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Overdose of the over the counter analgesic acetaminophen (APAP) is associated with hepatic damage. Previous work form our laboratory and by others have shown that S-adenosyl-L-methionine (SAMe) is protective for APAP induced hepatotoxicity. This study tested the hypotheses that: 1) SAMe reduces APAP mediated oxidative stress by maintaining glutathione peroxidase activity and 2) SAMe treatment prevents APAP mediated decline in total hepatic SAMe levels. Male C57BL/6 mice (16-25 g) were randomly divided into 4 groups (n=5/group): Vehicle (VEH), SAMe, APAP and SAMe+APAP. Mice were fasted overnight, injected intraperitoneal (ip) with water (VEH; 5ml/kg) or 250 mg/kg APAP (15 ml/kg) followed 1h later by ip injection of 1.25 mmol/kg SAMe. Plasma and liver were collected 4 or 6h after APAP administration. SAMe treatment did not alter hepatic function as plasma ALT and liver weight (wt) were comparable to VEH values. APAP administration increased plasma ALT levels and hepatic liver wt. when compared to VEH and SAMe groups confirming hepatic toxicity. Hepatic glutathione peroxidase activity was diminished ($p<0.05$) 4 and 6 h after APAP injection compared to VEH. APAP mediated decline in hepatic glutathione peroxidase activity was partially corrected at 4 hr in the SAMe+APAP when compared to the APAP treated mice. Total hepatic SAMe levels were diminished 4 h after APAP treatment when compared to the VEH and SAMe groups. Depletion of total hepatic SAMe levels was prevented